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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,364	05/25/2001	Saburo Sone	04853.0071	1599
22852	7590	02/25/2004	EXAMINER	
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP 1300 I STREET, NW WASHINGTON, DC 20005			LI, QIAN JANICE	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S-114

Office Action Summary**Application No.**

09/864,364

Applicant(s)

SONE ET AL.

Examiner

Q. Janice Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5,7,9-19 and 21-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5,7,9-19 and 21-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 May 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12/1/03 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/1/03 has been entered.

Claims 1, 2, 10, 11, 19 have been amended. Currently, claims 1-5, 7, 9-19, and 21-25 are pending and under examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 9-19, 21-25 stand rejected and the rejection has been modified under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a rodent bone metastasis model animal by intravenous administration of human lung small cell carcinoma cell line SBC-5 cells, wherein the rodent is immunodeficient, does not reasonably provide enablement for producing a rodent bone metastasis model animal by intramuscle, intracutaneous, subcutaneous, and intraperitoneal administration of *any* cancer or tumor cells that highly express PTHrP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

With respect to the type of immunodeficient rodents, it is noted that "immunodeficiency" was defined as "*inability* to produce a normal complement of antibodies or immunologically sensitized T cells especially in response to specific antigens" (Merriam—Webster's Online Dictionary). In view of the definition and applicants' arguments, the rejection to immunodeficient rodent is withdrawn. However, claims 13-16 are drawn to a rodent with a reduced immunity rather than immune deficient, thus, the rejection remains applicable to these claims.

With respect to the type of tumor cells, applicants argue that they have amended claims to recite "tumor cells that induce bone metastasis and highly express PTHrP", and the specification provides guidance as to determine whether the tumor cells highly express PTHrP.

The arguments have been fully considered but found not persuasive because the specification fails to teach the causative relationship of PTHrP and bone metastasis for any tumor cell that expresses high levels of PTHrP. In fact, quite a few prior art of record have concluded that PTHrP expression is not necessary or correlated with the bone metastasis. For example, *Guise et al* (J Bone Min Res 1994;9:S128) teach that increased PTHrP could enhance osteolytic metastases, but low PTHrP breast cancer cells could exhibit bone metastasis as well. *Rabbani et al* (Int. J Cancer 1999 ;80 :257-64) teach that prostate cancer cells transfected with PTHrP (highly express PTHrP) did not exhibit bone (skeletal) metastasis by subcutaneous administration, whereas by intracardiac injection, the same type of cells would exhibit bone metastasis with or without high PTHrP expression (e.g. abstract, and fig. 3). It appears that the skeletal invasiveness is more relevant to the route of administration rather than the levels of PTHrP. *Blomme et al* (The Prostate 1999;39:187-97) teach, "PTHrP OVEREXPRESSION BY MATLYLU CELLS WAS NOT ASSOCIATED WITH ANY DIFFERENCE IN THE INCIDENCE OF BONE METASTASIS, SIZE OF METASTATIC FOCI OR TUMOR-CELL PROLIFERATION" (abstract, emphasis added). In view of such, the claims do not appear to be enabled commensurate with their scope.

With respect to the routes of administration, the specification only illustrates bone metastasis of human lung small cell carcinoma cell line SBC-5 cells via intravenous administration, whereas claims encompass intramuscular, intracutaneous, subcutaneous, and intraperitoneal administration. Turning to the state of the art, *Yoneda et al* (US 5,993,817) teach that mice inoculated with MDA231 cells by left ventricle developed osteolytic lesions whereas intramuscular inoculation only developed local tumors (column 8, lines 9-19). *Rabbani et al* (Int. J Cancer 1999 ;80 :257-64) and *Blomme et al* (The Prostate 1999;39:187-97) have shown that subcutaneous injection fails to induce bone metastasis while intracardiac injection of the same cells did no matter whether PTHrP is highly expressed. *Dougherty et al* (Cancer Res 1999;59:6015-22) teach that subcutaneous administration fails to induce skeletal metastases even though the PTHrP is highly expressed (PTHrP-plasmid transfected cells, § bridging left & right columns). In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references.

For reasons of record and set forth foregoing, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph commensurate with the scope of claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7, 9-19, 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of claim recitation, "highly express PTHrP". The specification fails to define what levels of expression is considered "high", thus, the metes and bounds of the claims are unclear.

Claims are vague and indefinite because of claim recitation, "in which" (line 2 of claims 1), it is unclear what "which" refers to, e.g. bone, tumor cells or the animal, and thus the metes and bounds of the claims are unclear.

Claims are vague and indefinite because of claim recitation, "tumor cells that induce bone metastasis" (claims 1, 10). It appears that the tumor cells would develop bone metastasis rather than induce bone metastasis.

Claims 13, 14, 15, and 16 recite the limitation, "the step of providing a rodent having reduced immunity". There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

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granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The prior rejection of claims 1, 2, 4, 5, 10, 11, 24, and 25 under 35

U.S.C. 102(b) as being anticipated by *Engebraaten et al* (Int J Cancer 1999;82:219-25)

is withdrawn in view of claim amendment excluding intracardial injection.

The prior rejection of claims 1, 4, 5, 7, 9, 10, 13-15, and 21-25 under 35

U.S.C. 102(e) as being clearly anticipated by *Sawyers et al* (US 6,365,797) is

withdrawn in view of claim amendment and because by subcutaneous injection of a single cell suspension of prostate tumor cells, no bone metastasis was induced as shown in examples 2 and 3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The prior rejection of claims 10, and 16-18 under 35 U.S.C. 103(a) as being unpatentable over *Sawyers et al* (US 6,365,797), and in view of *Yano et al* (Intl J Cancer 1996;67:211-17) is withdrawn in view of claim amendment and because by

subcutaneous injection of a single cell suspension of prostate tumor cells, no bone metastasis was induced as shown in examples 2 and 3.

Claims 1, 2, 4, 5, 7, 10, 11, 19, 21, 24, and 25 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Lelekakis et al* (Clin Exp Metastasis 1999 Mar;17:163-70).

Lelekakis et al teach a mouse model of bone metastasis, wherein a single cell suspension of spontaneous arising mammary carcinoma cell line 4T1.2 was introduced to female Balb/c mice by intravenous (lateral tail vein) and mammary fat pad injection (e.g. right column, page 164), wherein by day 20 post-injection, the metastases were observed in the animals' own lung and vertebrae bone (e.g. right column, page 165), wherein the cells highly express PTHrP (fig. 3). *Lelekakis et al* also teach that the model is useful for the development of new therapies for metastatic breast cancer (abstract). *Lelekakis et al* do not use an immunodeficient animal, but reviewed the art-known bone metastatic animal model for studying breast cancer in immunodeficient mice (e.g. paragraph bridging pages 163-4), and teach of the advantage of their model is closely resemble the naturally occurring metastatic breast cancer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the cell line taught by *Lelekakis et al* in establishing breast cancer metastasis by intravenous administration either to normal balb/c mice or the conventional immunodeficient mice with a reasonable expectation

of success because if the spontaneous arising carcinoma cells could develop multi-organ and bone metastases in immunocompetent mice, they would be reasonably expected to develop such metastases in an immunodeficient mice. It would also have been obvious to one of ordinary skill in the art to use the model for new drug screening. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.


Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

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JANICE LI
PATENT EXAMINER


Q. Janice Li
Patent Examiner
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February 23, 2004